Pharmacokinetics, Pharmacodynamics and Safety of Rusfertide, a hepcidin mimetic, in Subjects with Hepatic Impairment and in Subjects with Renal Impairment

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Introduction

- Rusfertide is a synthetic peptide mimetic of the natural hormone hepcidin and binds to the ferroportin receptor.
- Rusfertide is currently in clinical investigation for the treatment of polycythemia vera.
- Rusfertide undergoes hydrolysis and proteolysis to two major metabolites, M4 and M9.
- Cytochrome P450 isozymes do not appear to play an important role in rusfertide metabolism.
- Following subcutaneous administration, rusfertide concentrations in urine were below the limit of quantitation, suggesting rusfertide is not renally cleared.

Objectives

- Evaluate rusfertide pharmacokinetics and pharmacodynamics in subjects with renal impairment and with hepatic impairment.
- Characterize the tolerability and safety of rusfertide.

Methods

Study Design

- Open-label, single dose, reduced design study
  - Control group with normal organ function was matched to mean age and weight of the impaired organ function groups
- Eight subjects with severe renal impairment (eGFR <30 mL/min/1.73 m^2 and not on dialysis) and 8 subjects with moderate hepatic impairment (Child Pugh B; score of 7-9) were enrolled.

Treatment

- Single subcutaneous dose of 20 mg rusfertide.

Pharmacokinetic Assessments

- Plasma samples were collected for up to 216 hours for measurement of rusfertide and its 2 major metabolites, M4 and M9.
- Pharmacokinetic parameters (C_{max}, $t_{1/2}$, CL/F, AUC, and AUC ratios) were estimated

Pharmacodynamic Assessments

- Blood samples were collected for up to 96 hours for measurement of serum iron and transferrin-iron saturation (TSAT).

Safety

- Adverse event (AE) monitoring, laboratory evaluations, vital signs, physical examinations, and electrocardiogram

Results

Study Population

- Eight subjects were enrolled in each study group. Study demographics are summarized in Table 1.
- All enrolled subjects completed the study

Rusfertide Pharmacokinetics

- Rusfertide plasma concentration-time profiles are presented in Figure 1.
- Mean AUC_{inf} and C_{max} in subjects with severe renal impairment were 12% and 36% higher, respectively, compared to healthy controls (Figure 2)
- Mean AUC_{inf} and C_{max} in subjects with moderate hepatic impairment were 34% and 23% lower, respectively, compared to healthy controls (Figure 2)
- There was no difference in elimination half-life between study groups

Rusfertide Pharmacodynamics

- Serum iron and TSAT decreased rapidly following rusfertide in all 3 treatment groups.
- Similar reductions from baseline in mean serum iron concentrations (7-9 µmol/L) and TSAT (10%-12%) were seen in all 3 groups (Figure 3).

Safety

- Subcutaneous rusfertide 20 mg was well tolerated
  - No subject reported any treatment-emergent adverse events (TEAEs) that led to discontinuation
  - Each type of TEAE was only seen in 1 subject
  - One healthy subject (13%) had bilirubin increased
  - In the hepatic impairment group, 1 subject (13%) each had abdominal pain, injection site erythema, injection site pain, and ligament sprain.

Table 1. Subject baseline characteristics

	Healthy Subjects	Severe Renal Impairment	Moderate Hepatic Impairment	All Subjects
Enrolled, N	8	8	8	24
Female, n (%)	2 (25)	2 (25)	1 (13)	5 (21)
Race, n (%)				
Black	0	1 (13)	1 (13)	2 (8)
White	8 (100)	7 (88)	7 (88)	22 (92)
Age (y)	57.6±4.9	59.1±11	63.3±10	60.0±8.9
Weight (kg)	90.4±5.4	88.4±13	85.9±11	88.3±10
BMI (kg/m^2)	29.1±1.6	32.0±4.4	29.0±3.0	30.3±3.4
eGFR mL/min/1.73 m^2	97.8±2.9	18.3±6.6	93.1±18.3	69.7±38.8

Data reported are mean±SD unless specified otherwise

Table 2. Summary of Rusfertide Pharmacokinetics

	Healthy Subjects (N=8)	Severe Renal Impairment (N=8)	Moderate Hepatic Impairment (N=8)
C_{max} (ng/mL)	185 (194, 33)	251 (258, 24)	143 (152, 41)
T_{max} (h) [a]	24 (4, 48)	18 (4, 48)	16 (4, 36)
$t_{1/2}$ (h)	30.8 (32.7, 36)	31.1 (33.5, 44)	35.6 (38.1, 41)
AUCinf (ng·h/mL)	16900 (17200, 20)	19000 (19300, 20)	11100 (11700, 37)
CL/F (L/h)	1.18 (1.21, 22)	1.06 (1.07, 19)	1.80 (1.88, 29)
AUC_{Rusf}/AUC_{Total} (%)	54.9 (55.0, 5.6)	48.4 (48.7, 11.4)[b]	44.7 (44.9, 10.5)[b]
AUC_{M4}/AUC_{Total} (%)	14.5 (15.1, 28.6)	8.2 (9.1, 48.0)[b]	12.4 (13.0, 32.0)[b]
AUC_{M9}/AUC_{Total} (%)	29.8 (29.9, 7.9)	41.3 (42.3, 21.0)[b]	41.8 (42.0, 10.7)[b]

Data reported are geometric mean (arithmetic mean, %coefficient of variation), unless specified otherwise
[a] median (min, max)
[b] N=7

Figure 1. Rusfertide Pharmacokinetics. Data presented are geometric mean.

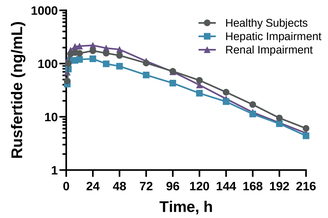


Figure 2. Forest plots of ratio of geometric mean and 90% confidence interval for C_{max} and AUC_{inf}

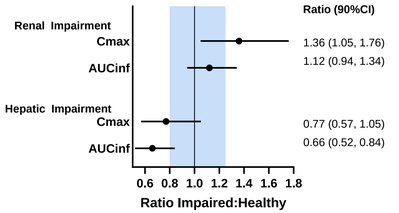
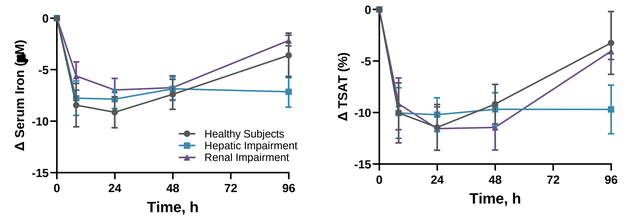


Figure 3. Change in (a) serum iron, (b) TSAT Data presented are mean and standard error



Discussion

- Differences of <2-fold in C_{max} and AUC_{inf} were noted in severe renal or moderate hepatic impairment compared to subjects with normal organ function
- Rusfertide is titrated to effect based on hematocrit response; no dose adjustments are needed in patients with severe renal impairment or with moderate hepatic impairment.
- Pharmacodynamic effects on serum iron and TSAT were similar in all three groups.

Conclusions

- Severe renal impairment or moderate hepatic impairment did not have a clinically meaningful effect on rusfertide pharmacokinetics or pharmacodynamics.
- Rusfertide 20 mg was well tolerated by subjects with severe renal impairment or with moderate hepatic impairment and by healthy subjects.

References

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